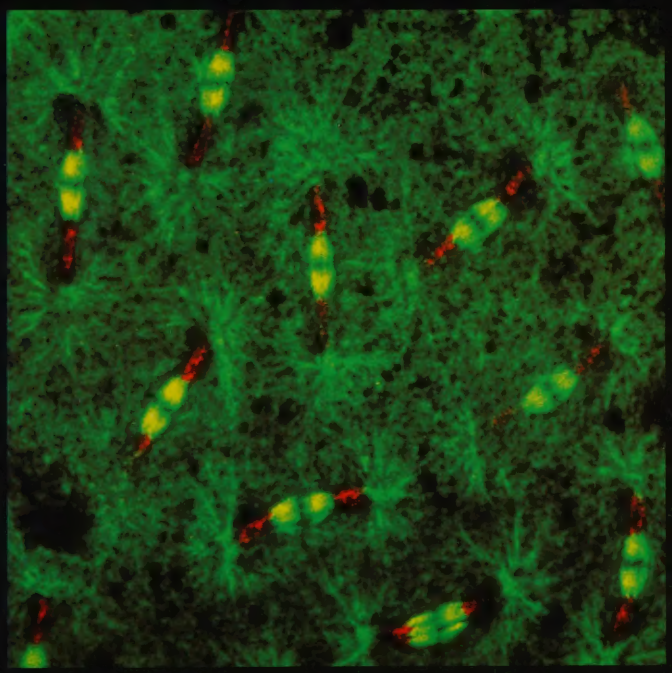
THE WELLCOME TRUST
Institute of Cancer and Developmental Biology
CANCER RESEARCH CAMPAIGN

1998



THE WELLCOME / CRC INSTITUTE
UNIVERSITY OF CAMBRIDGE



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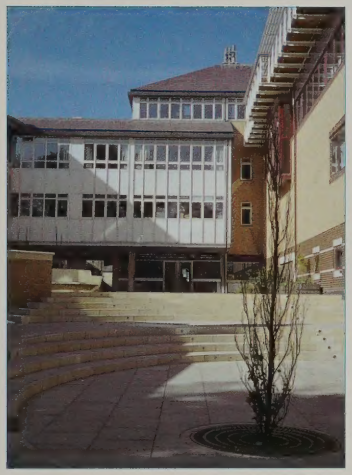
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Front cover photograph
Microtubules (Green) and Chromatin (Red) at telophase in an early *Drosophila* embryo.



WITHIN THE INSTITUTE

The Institute consists of seventeen independent research groups containing postdoctoral scientists, visitors, research assistants and a total of more than 50 graduate students. Together with support staff, the Institute comprises 200 personnel, all of whom are affiliated, through their group leaders, to one of the University science departments. The teaching we do and our lists of publications are credited to our parent departments, and we have access to their workshops and equipment.

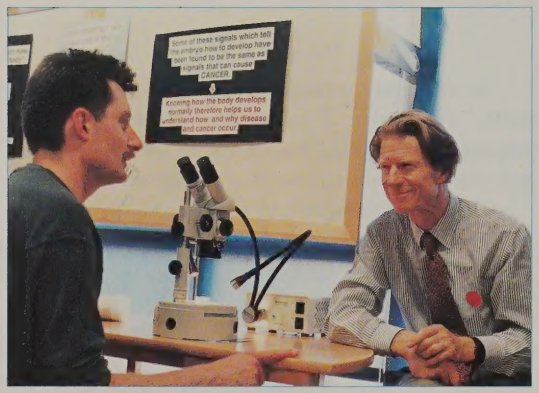
We receive funding in a 2:1 ratio from our major sponsors, the Wellcome Trust and the Cancer Research Campaign. Research grant expenditure approached six million pounds for the year 1996/97 and examples of awards received over this period, given below, highlight the type of funding available to individuals in the Institute.



The Wellcome Trust awarded Programme Grants to Azim Surani and Martin Evans, a new Principal Research Fellowship to Daniel St Johnston, and a Career Development Fellowship to Nancy Papalopulu. CRC support has included 'Core' grants for tissue culture facilities, a DNA sequencer and general equipment in addition to funding for investigating the application of basic research strategies to cancer problems. Five-year Fellowships from the Lister Institute of Preventive Medicine, the Royal Society and the BBSRC (a David Phillips Fellowship) have also been awarded to senior postdoctoral workers.



In October 1997, Michael Akam, one of our senior group leaders was appointed as Professor of Zoology and Director of the University Museum of Zoology. Tony Kouzarides received the 1996 Bodassaki Prize for Biology and Steve Jackson, the Tenovus Scotland Medal for major contributions to understanding of eukaryotic gene expression. Ron Laskey received the Biochemical Society's CIBA medal and was awarded the Feldberg Prize and the 1998 Louis Jeantet Prize for Medicine (Switzerland). (Other recognitions are listed on page 51.)

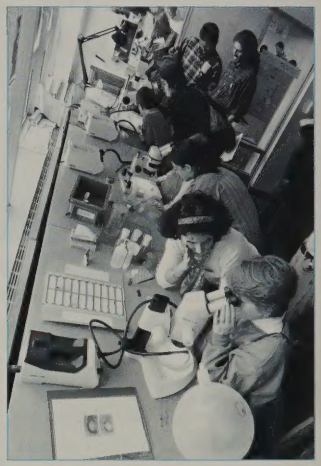


The Institute participated in National Science Week for the first time in 1997, opening its doors to Cambridge residents and visitors, and staging visual, audio and practical demonstrations of the research work currently in progress.



HISTORICAL BACKGROUND

The Institute is situated in the middle of the area containing the science departments of the University of Cambridge and within a short distance of the centre of the historic city. It was founded in 1989 to promote research in the areas of Developmental Biology and Cancer Biology and is an assemblage of independent research groups located in one building designed to promote as much interaction as possible. Developmental and cancer biology are complementary since developmental biology is concerned with how cells come to acquire and maintain their **normal** function; cancer is a result of a cell breaking loose from its correct controls and becoming ***abnormal***. Both areas require a detailed knowledge of intracellular processes, which need to be analyzed at the cellular and molecular levels.



These research areas are complementary at the scientific and technical levels. To understand what goes wrong when a cell becomes cancerous requires a knowledge of the processes which ensure correct cell function in normal development. At the technical level, the analysis of cellular and molecular processes requires familiarity with techniques which no one person can master, such as gene cloning, antibody preparation, cell culture, and embryological manipulation. There is, therefore, a major benefit in having scientists with different but complementary knowledge and technical skills working in close proximity to one another.

John Gurdon.

John Gurdon *Chairman*



We are fortunate to have excellent core funding available to provide the necessary central services that support the individual research groups in the Institute. It has proved a significant advantage to have central funding for the larger items of equipment (eg centrifugation, confocal microscopy, histology, oligo synthesis and computer graphics) used communally. The aim of the small group of core staff is to support the groups' research by reacting quickly to necessary changes in group requirements and central facilities, eg increases in staff, alterations to laboratories, reorganization or purchase of equipment.

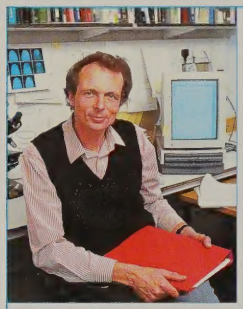
Grant-funded research within a University environment inevitably entails significant amounts of paperwork and organization: grant applications, financial management, appointments, setting up of labs and purchase of consumables and equipment. Core support is there to ensure that the researchers workload in these areas is kept to a minimum. In addition to scientific, social and sporting facilities provided by membership of University Science Departments and the Cambridge colleges, all in the Institute benefit from events organized by enthusiastic members of staff. This year these have included wine and whisky tastings, football, rounders, the annual Cambridge Chariots of Fire race and the Institute scientific two-day retreat.







MICHAEL AKAM



GUILLLAUME BALAVOINE

SUSAN BEGG

CHUN-CHE CHANG

CHARLES COOK

OLENKA DUNIN-BORKOWSKI

PHILIPPE GAUTIER

MIODRAG GRBIC

CHRISTEN MIRTH

FERNANDO ROCH

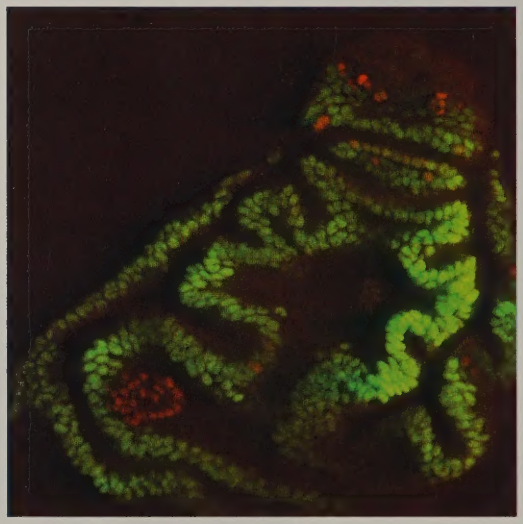
MARION ROZOWSKI

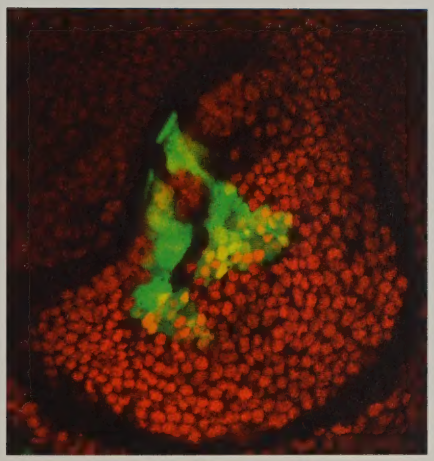
LOUISE SMITH

DAVID STERN

BEVERLEY YEN

Confocal optical section of a Drosophila leg disc showing the modulated expression of Ubx protein (green) in the disc epidermis. Developing sensory cells (red) provide landmarks in the disc. (Marion Rozowski)





A clone of cells in the developing Drosophila wing engineered to express both Ubx and green fluorescent protein. (Fernando Roch)

Over the last ten years, it has become clear that all animals use a very similar 'toolkit' to build their embryos, and yet they exhibit enormous diversity – of developmental processes and of body plans. We use the extensive understanding of Drosophila development as a starting point, from which to explore the jungle of arthropod diversity.

One focus of our interest is the diversity of development itself. Many insects appear to make their embryos in very different ways from Drosophila. For example, the germ line of Drosophila is specified very early, by the segregation of maternal determinants. In other insects, the germ line has only been identified much later, and may be specified by induction in the forming gonads. Is this difference real, or only apparent? Using the vasa gene product as a conserved molecular marker for the germline in locusts, we are re-examining when and where germ cells are first formed, and what is necessary for their specification.

Much of our work focuses on the genes of the Hox cluster, which control the diversification of arthropod segments. Changes in the regulation of Hox genes have played a significant role in insects and crustaceans – for example, in the specialisation of thoracic segments to form maxillipeds in many groups of Crustacea.

To understand this process in more detail we are examining how the Hox genes affect the development of the legs and wings in Drosophila. We find that the regulation of the Hox genes within segments controls details of the cuticular pattern – for example the pattern of trichomes in the legs. Subtle differences between closely related species of Drosophila depend in part on changes at the Ubx locus, suggesting that even these 'master control genes' contribute to gradual evolutionary change.

In 1998 our research group will move to the University Museum of Zoology, following Michael Akam's appointment as its Director.

Averof, M. and Akam, M. (1995). Hox genes and the diversification of insect and crustacean body plans. **Nature 376, 420-423.**

Ho, K., Dunin-Borkowski, O. and Akam, M. (1997). Cellularisation in locust embryos occurs before blastoderm formation. **Development 124, 2761-2768.**

ENRIQUE AMAYA



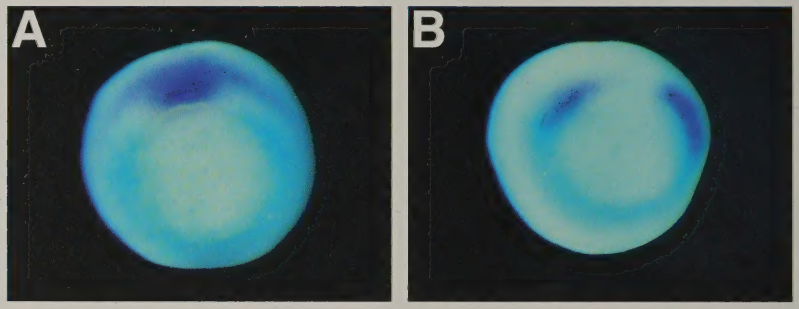
ROSS BRECKENRIDGE

ODILE BRONCHAIN

MIRANDA GOMPERTS

KATHARINE HARTLEY

MATTHEW POLLI

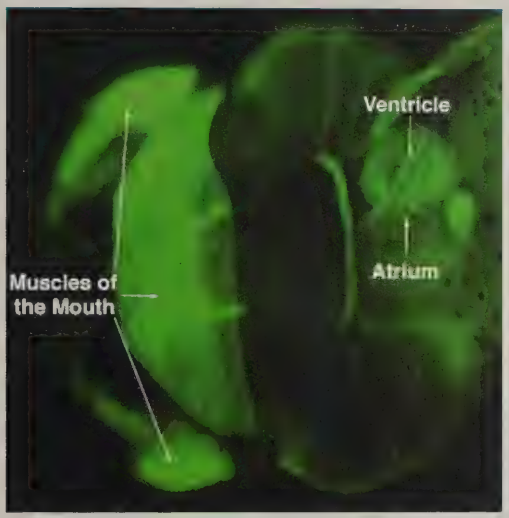


Gastrula stage embryos stained for the expression of Xwnt8 (light blue in panels A and B) in relation to the expression of Xnot (dark blue in panel A) and Xmyf-5 (dark blue in panel B). Xwnt8 is a signalling molecule expressed in lateral and ventral mesoderm. Xnot is a gene expressed in dorsal mesoderm fated to become notochord. Xmyf-5 is a myogenic gene expressed in dorsal-lateral mesoderm fated to become muscle.





Transgenic tadpole expressing green fluorescent protein (GFP) under the control of a lens specific promoter. Panel A shows a low magnification image of a transgenic tadpole viewed under a combination of blue and normal white light. Panel B shows a high magnification image of the eye of a transgenic tadpole viewed under normal white light.



Ventral view of the head and thorax of a transgenic tadpole expressing green fluorescent protein (GFP) in all its muscles

The vertebrate embryo is organized and patterned following a series of inductive events. The first of these signalling events results in the induction of the mesoderm at the blastula stage. The second event occurs at the gastrula stage when the mesoderm becomes patterned. As a long term goal we would like to understand the molecular basis of the inductions that organize the vertebrate embryo. In addition, we would like to better understand how localised production of signalling molecules becomes translated into organized changes in cell movement and differentiation.

To this end we have been investigating the role of fibroblast growth factor (FGF) during mesoderm formation in the frog, Xenopus laevis. We have found that inhibiting FGF signalling in the embryo, by expressing a dominant negative version of the FGF receptor, disrupts mesoderm formation. We are now investigating the role of antagonising signals in establishing pattern within the mesoderm during the gastrula stages. In addition, by following the morphogenetic movements that occur during the gastrula and neurula stages using time-lapse video microscopy, we hope to better understand how signals affect morphogenesis.

We recently developed a very efficient method for making transgenic frog embryos. This technology enables us to manipulate the expression of developmental genes in the embryo with much better precision than ever before. It also allows us to investigate the regulation of promoters in a developmental context. Finally we are evaluating whether the transgenesis method can be adopted for insertional mutagenesis in frogs.

Kroll, K.K. and Amaya, E. (1996) Transgenic Xenopus embryos from sperm nuclear transplantations reveal FGF signalling requirements during gastrulation. **Development 122:3173-3183**.

McFarlane, S., Cornel, E., Amaya, E. and Holt, C.E. (1996) Inhibition of FGF Receptor Activity in Retinal Ganglion Cell Axons Causes Errors in Target Recognition. **Neuron 17:245-254**.

Amaya, E. and Kroll, K.K. (1997) A method for generating transgenic frog embryos. In **Methods in Molecular Biology: Molecular Embryology: Methods and Protocols**. Edited by Paul Sharpe and Ivor Mason. **Humana Press Inc. , Totowa, NJ., in press**.

ANDREA BRAND



TORSTEN BOSSING

CATHERINE DAVIDSON

EMMA LOUISE DORMAND

NEIL HAYWARD

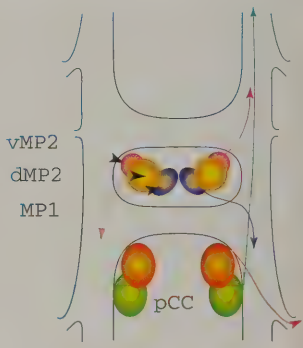
ULRIK JOHN

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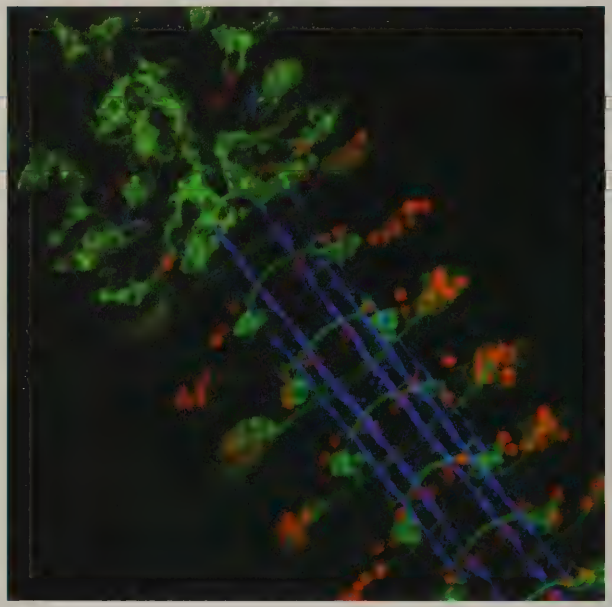
TRINIDAD LEI

[redacted]

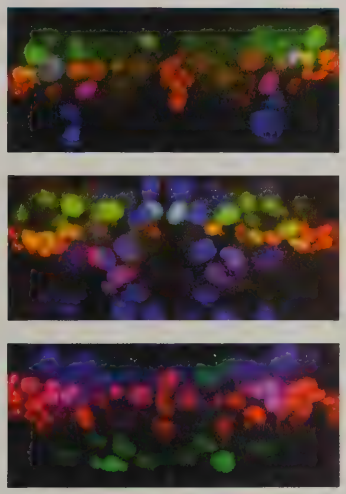
ALISON SCHUELDT



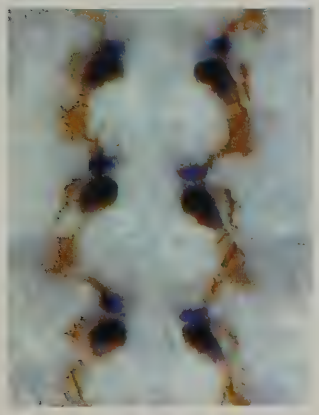
The pioneer neurons, MP1, dMP2, vMP2 and pCC, act as a group to establish the longitudinal axon tracts and to organise follower neurons into distinct fascicles.



Targeted expression of Tau GFP (green) labels individual neurons as they extend their axons in the central nervous system of living embryos. Tau-GFP continues to fluoresce after fixation, which allows immunolabelling of other proteins, such as Even-skipped (red) and Fasciclin II (blue).



Neural precursor cells can be identified by their characteristic patterns of gene expression, as detected by confocal microscopy.



A subset of motor neurons and interneurons express Even-skipped (in the nucleus) and Fasciclin II (at the membrane) during axonogenesis.

During nervous system development each neuron acquires a specific identity, directing it to extend an axon towards and synapse with an appropriate targét cell. Cell identity is acquired in response to a specific pattern of gene expression and to cell-cell interactions. We have developed a method for directed gene expression in *Drosophila*, the GAL4 system, that allows transcription to be manipulated both spatially and temporally. Using targeted gene expression, transcription patterns in neuronal precursor cells and in their progeny can be altered with the aim of eliciting specific cell fate changes. In this way, we are investigating the role of segmentation genes in directing neuronal and glial cell fates.

One mechanism for generating cell diversity is to ensure that, upon cell division, each daughter cell assumes a different fate. This can be achieved through the asymmetric segregation of cell fate determinants. We are investigating the role of Staufen, a double stranded RNA binding protein, in directing the asymmetric segregation of cell fate determinants during neural cell divisions.

We have expressed toxins in a restricted fashion to ablate cells and eliminate the cell-cell interactions that influence cell identity and direct axon outgrowth. Targeted cell ablation has been used to assay the role of glial cells and pioneer neurons in establishing the axon scaffold. We have also killed specific subsets of the ventral midline cells, which send out attractive or repulsive signals to migrating axons. For this reason the midline cells are thought to be analogous to the vertebrate floorplate.

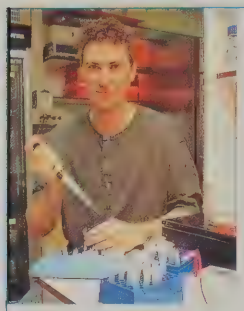
To monitor the effect of cell ablation and cell fate changes in vivo, we are labelling neurons and glia in living embryos by expression of green fluorescent protein (GFP) from the jelly fish, *Aequoria victoria*. We can now assay cell fate determination and cell-cell interaction in vivo, tracing individual cells through development.

Hidalgo, A. and Brand, A. H. (1997). Targeted neuronal ablation: the role of pioneer neurons in guidance and fasciculation in the CNS of *Drosophila*. **Development 124, 3253-3262.**

Brand, A.H. (1995) GFP in *Drosophila*. **Trends in Genetics 11, 324-325.**

Hidalgo, A., Urban, J. and Brand, A.H. (1995) Targeted ablation of the longitudinal glia disrupts axon tract formation in the *Drosophila* embryonic CNS. **Development 121, 3703-3712**

NICK BROWN



INES ALVAREZ-GARCIA

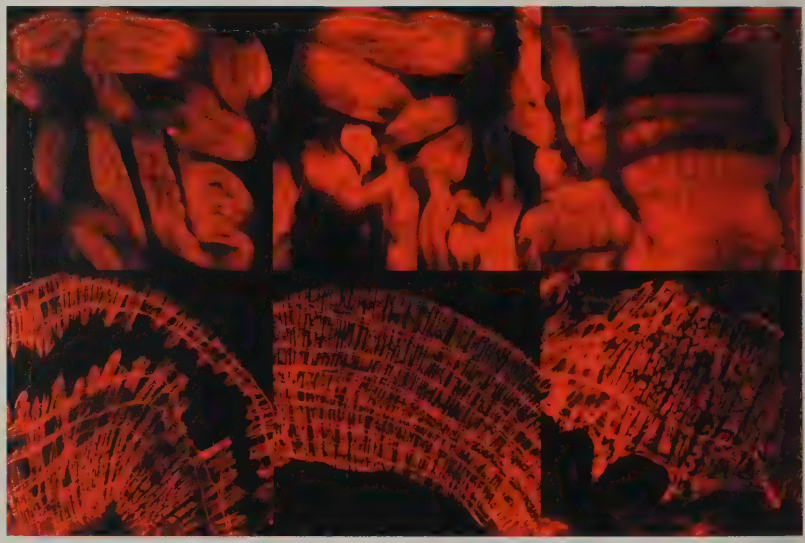
STEPHEN GREGORY

ANDREA KNOX

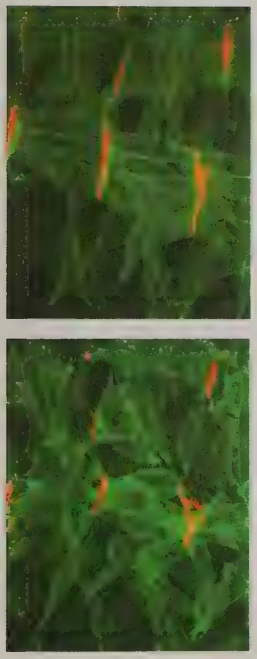
ANNE MAELAND

LOLA MARTIN-BERMUDO

JOHN OVERTON



Different classes of mutation in the integrin αPS2 subunit have different effects on the somatic muscles (top) and visceral muscles surrounding the midgut (bottom). The muscles are stained for actin with phalloidin coupled to rhodamine. The class I mutation (left) weakly affects both, the class II (middle) just the somatic muscles and the class III (right) just the visceral muscles



The complete absence of the PS2 integrin causes detachment of the muscles (outlined in green) from the tendon matrix (labelled in red) in the developing embryo. The top panel shows a wild type embryo while the bottom shows an embryo lacking the PS2 integrin

The development of multicellular organisms requires the activity of a variety of cell surface proteins that mediate adhesion and signalling between cells. We are particularly interested in the link between cell adhesion and signalling, and our current efforts are focused on elucidating the role of integrin cell surface receptors in these processes, using two general approaches. One is to modify the integrin molecules and assay their function in the developing animal. The second is to use the genetic methods available in Drosophila to identify the other molecules involved in integrin function, which we expect to include other cell surface proteins, cytoskeletal and extracellular matrix molecules and components of signalling pathways.

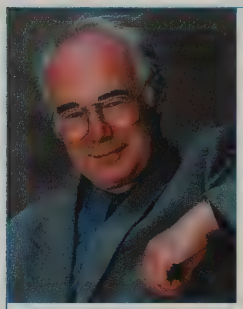
The two integrin heterodimers αPS1βPS and αPS2βPS are expressed in complementary tissues during embryogenesis. We have shown that this reflects a difference in the functions of the two α subunits, which reside in the extracellular domains. A classical genetic approach has isolated αPS2 mutations that inactivate subsets of this integrin's activities. One specifically affects the formation of muscle sarcomeres, while two others specifically block the morphogenesis of the gut and wing. Future work should determine if these mutations selectively block adhesion to specific ligands and/or sending of signals.

We have completed a screen of the Drosophila genome for mutations that are required for integrin mediated adhesion, and indentified 10 new genes. The first one of these that we have cloned encodes an extremely large cytoskeletal linker protein, indicating that the screen has successfully identified molecules likely to mediate integrin function.

Martin-Bermudo, M.D., Dunin-Borkowski, O.M. and Brown, N.H. (1997) Specificity of PS integrin function during embryogenesis resides solely in the α subunit extracellular domain. **EMBO J. 16, 4184-4193**

Bloor, J.W. and Brown, N.H. Genetic analysis of the Drosophila αPS2 integrin subunit reveals discrete adhesive, morphogenetic and sarcomeric functions. **Genetics, in press**

MARTIN EVANS



MARK CARLTON

ANDREAS RUSS

SUSAN HUNTER

MAGDALENA ZERNICKA-GOETZ

JOHN DIXON

VENKATA NARAYANA PISUPATI

EMILY SCOTT

GORDON STOTT

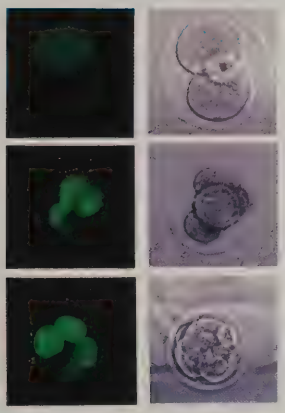
FIONA THISTLETHWAITE

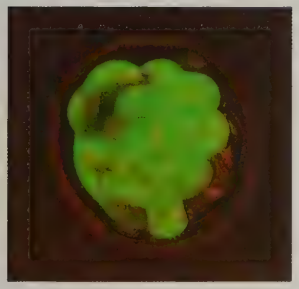
JOANNE WILSON

HELEN CHILVERS



An allele of Brca2 produced by gene targetting gives some small viable offspring with kinked tails and other skeletal abnormalities. Brca2-/- offspring at each end of their +/+ and +/- normal littermates. Overlaid over the picture of the mice is their growth in weight over 10 weeks. The homozygous mutants develop lymphomas in adulthood.





Our overall strategy and interest is in an Experimental Mammalian Genetics which is made possible through the use of embryonic (ES) cells of mice as a route to somatic and germ line transgenesis. Because these cells provide a bridge between the whole animal and tissue culture, specific genetic modification which may be induced, screened or selected in culture can be tested and recombined within the context of the physiology and genetics of the whole animal.

We are creating mouse mutants both by gene targeting and gene trapping to introduce specific mutations through ES cells into mice.

Genome projects with their rapid gene discovery are redefining classical genetic approaches. The efficient translation of this wealth of new information into insights in biological function at molecular, cellular and organismal levels does, however, require large-scale approaches to the generation of mutants. Gene trapping in (ES) cells should allow an efficient approach to the functional analysis of the murine genome. The usually separate processes of gene discovery, mapping, the observation of the expression pattern and the mutant phenotype in vivo, can be integrated by the use of an indexed library of insertionally mutated ES cell clones (below).

GFP is proving to be a very useful in vivo reporter in mice. Injection of one of the first two blastomeres allows observation of lineage and mixing during development of the blastocyst (left).

Zernicka-Goetz, M., ,Pines, J., McLean-Hunter, R, S., Dixon, J.P.C., Siemering, K., Haseloff, J., and Evans, M.J. 1997. Following cell fate in the living mouse embryo. **Development 124, 1133-1137**.

Evans, M.J., Carlton, M.B.L. and Russ, A.P. 1997 Gene trapping and functional genomics. **Trends in Genetics 13 370-374**



Map Position:	gene trap integration maps to locus of interest
Known Gene of Interest:	sequence identifies known gene not previously knocked out in mouse
GRAIL:	unknown gene predicted from genomic sequence
EST:	sequence matches Expressed Sequence Tags
Protein Sequence Homology:	translation of candidate exons reveals interesting protein motif
Expression Profile:	origin of ESTs identified indicates expression from specific tissue type or developmental stage
Sequence Uninformative:	no EST or other homology on databases (likely to become increasingly rare as databases expand)
***In vitro/vivo* Differentiation:**	differentiation of ES cell clone in culture or chimeric mouse shows expression in cell type of interest



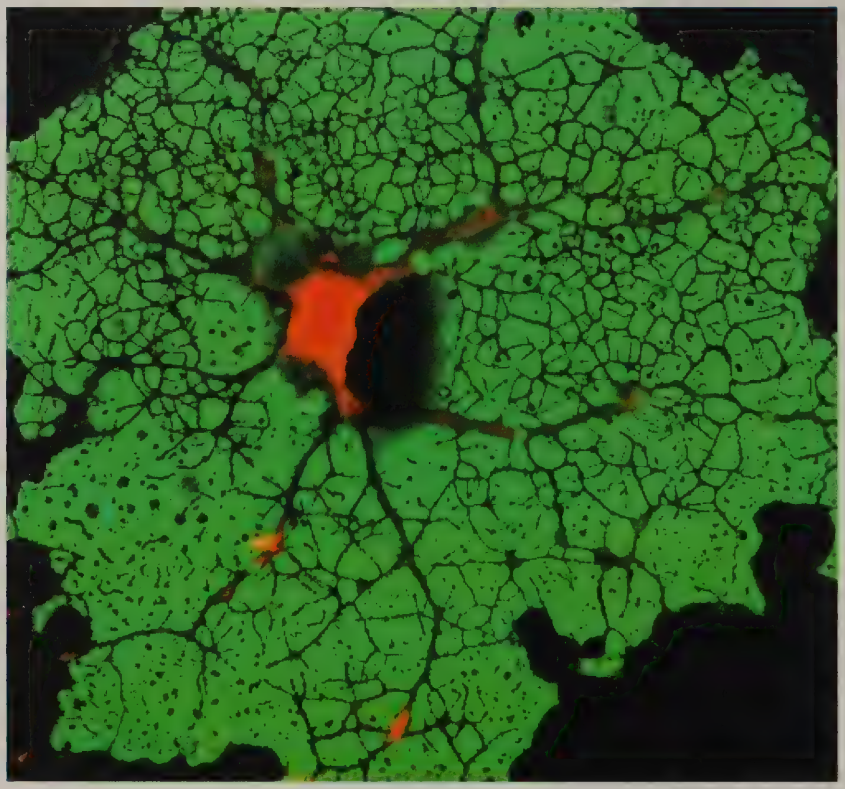
KATHERINE FASCHER

GILLIAN BUTLER

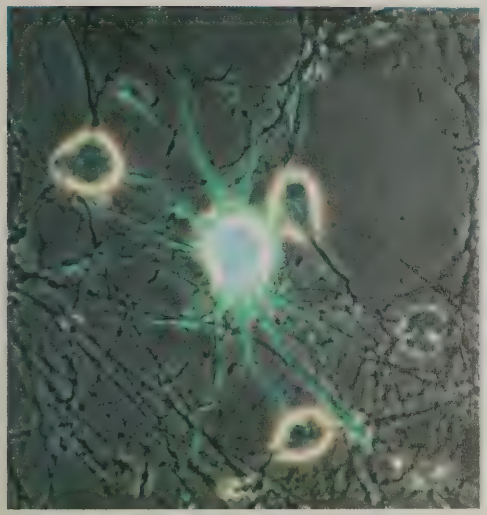
EMMA ROST

PAUL DEAS

MARTIN SCHILLING



Differentiated oligodendrocyte in cell culture



GFP – expressing oligodendrocyte precursor in co-culture

During the development of the CNS, committed progenitor cells form the different neural cell types from precursor cells in the ventricular and subventricular zones and then migrate to their final destinations prior to differentiation. Control of ventricular zone proliferation and progenitor cell migration is therefore essential for normal development, and a number of significant human neuro-developmental diseases arise from abnormalities in these mechanisms. The goal of the work in our lab is to elucidate the mechanisms of this control, and to do this we have examined cell matrix and cell/cell interactions in two cell types grown in cell culture systems, ventricular zone cells (grown as neurospheres) and committed progenitors of the oligodendroglial lineage.

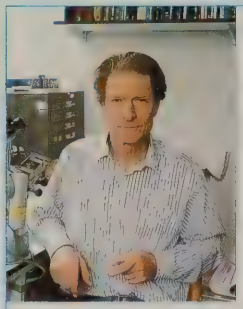
Our work on cell matrix interactions is focused on the integrin family of receptors. We have shown that each of the two cell types expresses a specific pattern of integrins, and that differentiation of oligodendrocyte precursors into myelin forming oligodendrocytes is associated with a switching of αv associated β subunits. Migration of the two cell types is mediated by different integrins; the homotypic cell/cell interactions responsible for ventricular zone chain migration requires α6β1 whilst oligodendrocyte precursor migration over substrates produced by different cell types requires αvβ1. As αvβ1 is lost as oligodendrocyte differentiation proceeds, this integrin may also play a role in determining the timing of migration.

In addition to cell matrix interactions, we have begun work on the role of cell/cell interactions following our observation that a protocadherin called fat (previously identified as a tumour suppresser in Drosophila) is expressed on ventricular zone cells. This suggests the hypothesis that this and other cadherins regulate proliferation as well as pattern in CNS development.

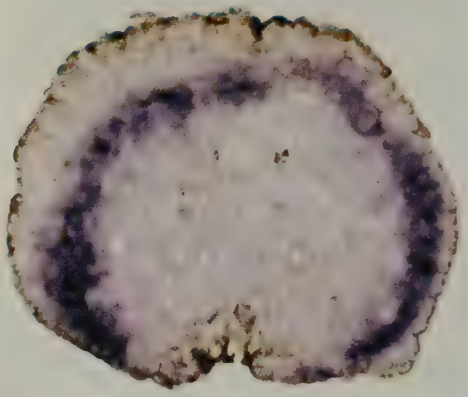
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JOHN GURDON



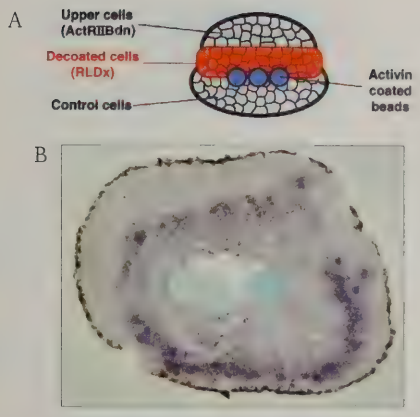
ERIC BELLEFROID
KAREN BUTLER
DEVANAND CREASI
STEVEN DYSON
NIGEL GARRETT
NATASHA McDOWELL
DHEVAHI NIRANJAN
KEN RYAN
HENRIETTA STANDLEY
FIONA STENNARD
ELIZABETH TWEED
CAROLINE WEBB
AARON ZORN



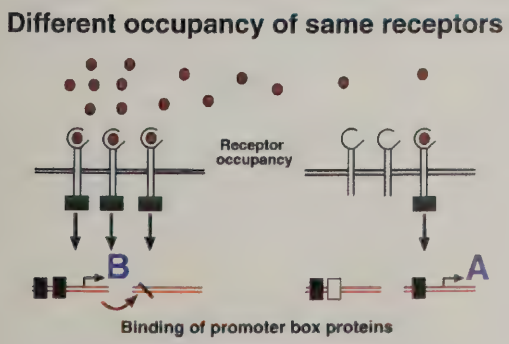
Activin spreads from a source at the bottom to create a concentration gradient, to which a ring of cells responds by activating Xbrachyury (purple).



A concentration gradient of ^{35}S-activin emanating from a bead (removed from the central space).



Activin behaves as a morphogen reaching distant cells, which require normal activin receptors.



A concept of how cells respond to morphogen concentration by activating different genes.

Signalling between cells is the single most important mechanism that brings about cell differentiation in Vertebrate development. In general, cells in one region of an embryo synthesize and secrete proteins that determine the path of differentiation of other nearby cells. In several cases, cells are now known to activate different genes according to the concentration of the same signalling molecule, which is therefore described as a morphogen.

We have developed methods of assembling cells into multilayered conjugates, in which a signalling source is supplied by a protein-containing bead. This provides us with an experimental system in which cells reveal their response to different concentrations of morphogen by expressing high or low response genes. We are analyzing the mechanism by which cells interpret their position in a morphogen gradient by constructing conjugates composed of cells that over- or under-express receptors that bind a ligand. We determine the number of receptors per cell and the proportion of these that are bound to their ligand, and relate this information to the type of gene response.

Another type of signalling in early amphibian development is the community effect in which several adjacent cells release a signal to which they respond when it exceeds a threshold concentration. This process enables cells to refine their early responses to a morphogen gradient by increasing uniformity within, and demarcation between, different cell types. We are actively engaged in a search for new genes responsible for these signalling events using a functional screen of subtracted cDNA libraries.

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STEVE JACKSON



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SIMON BOULTON

SUSAN CRITCHLOW

FABRIZIO D'ADDA DI FAGAGNA

DAMIEN D'AMOURS

JESSICA DOWNS

CHARLOTTE DUBERN

DANIEL DUROCHER

KNUT EICHHORN

RAIMUNDO FREIRE

DAVID GELL

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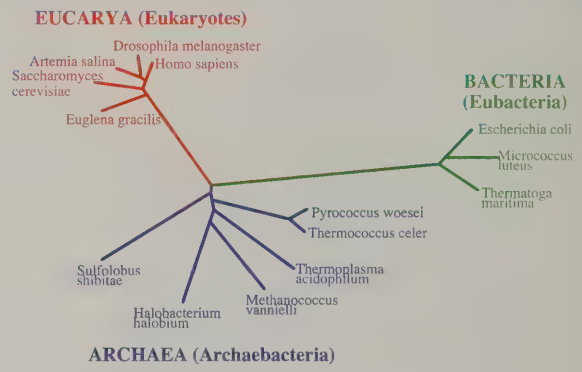
NICHOLAS LAKIN

ANDREW MCAINSH

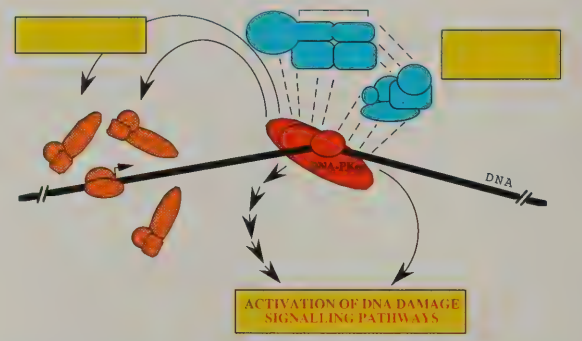
HELEN REED

GRAEME SMITH

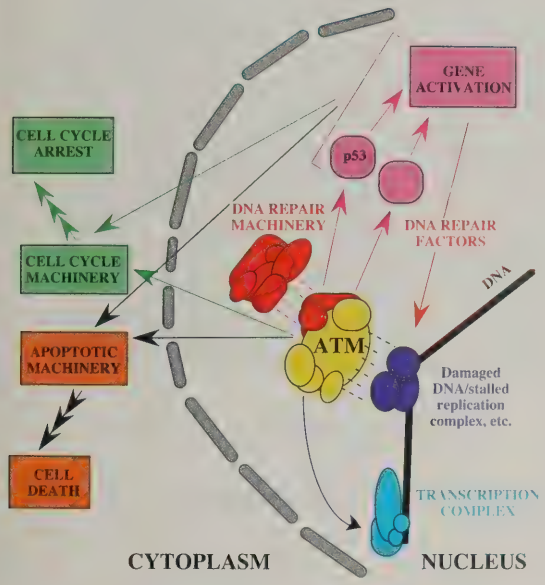
SOO-HWANG TEO



Archaea: the third domain of life. Despite lacking nuclei and being similar to eubacteria in morphology, Archaea are at least as distant evolutionarily from Bacteria as from Eucarya. Nevertheless, through cloning archaeal transcription factors and establishing a defined in vitro transcription system, we have discovered striking similarities between transcription in Archaea and in eukaryotic cell nuclei.



DNA-PK; A paradigm for DNA damage sensing systems. Model: DNA-PK binds to damaged DNA and potentiates DNA repair and V(D)J recombination through various mechanisms, as indicated. XRCC4 binds to the BRCT (BRCA1 C-terminal) homology region of DNA ligase IV and is depicted as recruiting ligase IV to the site of DNA damage.



The ATM-dependent DNA damage detection/signalling system. Model: ATM, in association with other proteins, recognises features such as DNA damage or stalled DNA replication forks. The activated ATM-associated signalling system then impinges on DNA repair, transcription, cell cycle control, and the apoptotic machinery.

We employ a diversity of approaches in bacterial, yeast and mammalian systems to investigate the molecular basis of transcription, cell cycle control, DNA repair and genetic recombination. For example, we have found that transcription in bacteria termed Archaea is strikingly similar to that in eukaryotic cells, and are using the unique biochemical advantages of Archaea to define the mechanisms and evolution of transcriptional control. In the mammalian system, we have learned that RNA polymerase III transcription is strongly cell cycle regulated and is targeted by the tumour suppressor proteins RB and p53.

We also study how cells detect, respond to, and repair DNA damage. Major focuses are the proteins Ku and DNA-PKcs which, together, recognise DNA double-strand breaks. We and others have shown that they function in repairing ionising radiation-induced DNA damage and are essential for V(D)J recombination, which helps generate the antigen binding diversity of the vertebrate immune system. We are characterising these factors and other components of the Ku-associated DNA repair system, including the proteins XRCC4 and DNA ligase IV. Our work has also helped establish that Ku plays additional roles in transcription, telomere length maintenance, transcriptional silencing and retrotransposition, and we are investigating the mechanistic basis for these effects. Finally, we are analysing proteins that are related to DNA-PKcs and also function in DNA damage detection – one being ATM, the protein deficient in the human cancer predisposition and neurodegenerative syndrome ataxia-telangiectasia. Through these studies, we aim to better understand how cells maintain genomic stability and how defects in this process can lead to cancer.

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ANDREW BANNISTER

ALEXANDER BREHM

[illegible]

FRANCOIS FUKS

LUKE HUGHES-DAVIES

KLAUS MARTIN

MARIAN MARTINEZ

JONATHAN MILNER

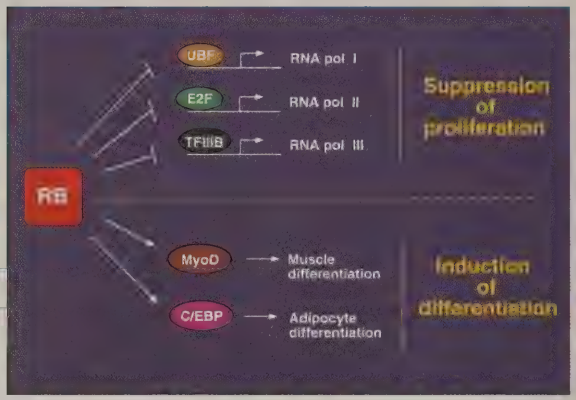
ERIC MISKA

SOREN NIELSEN

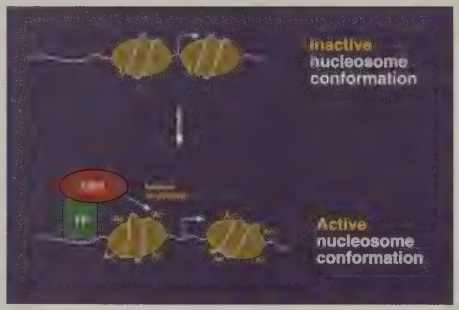
JULIET REID

MATTHIAS SELTMANN

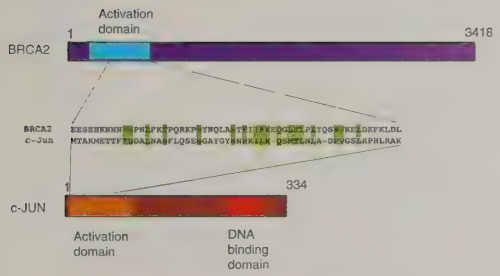
LAURENCE VANDEL



RB can repress pol I, II and III promoters via distinct targets and can stimulate specific transcription factors involved in differentiation.



The CBP co-activator stimulates transcription by acetylating nucleosomal histones and remodelling chromatin.



The BRCA2 protein has a transcriptional activation domain with similarity to c-Jun.

A number of transcription factors have been implicated in the generation of cancer. Our group is interested in defining the mechanisms by which such proteins modulate gene expression and regulate the proliferative state of the cell.

The Retinoblastoma gene is found mutated in a number of different cancers. Our analysis of the RB protein has revealed that this transcriptional repressor can silence RNA polymerase III genes as well as E2F-regulated RNA polymerase II genes. Suppression of protein biosynthesis may therefore contribute to the growth arrest functions of RB. Yeast two hybrid screens have identified other transcription factors targeted by RB. One of these is the HMG-box DNA binding protein HBP1 whose activation potential is masked by the binding of RB.

The CBP gene is found translocated in a specific subset of acute myeloid leukaemia's. The CBP protein has been termed a co-activator since it is able to bind and stimulate the activity of numerous DNA binding transcription factors. We recently made the unexpected discovery that CBP can acetylate histones, a property which would explain its co-activator functions. We are now investigating the precise mechanisms by which this enzymatic activity stimulates transcription.

The recently identified BRCA2 gene is found to be mutated in a substantial proportion of familial breast cancers. We find that BRCA2 has a potent transcriptional activation domain which shows sequence similarity to the activation domain of c-jun. A point mutation found in breast cancer disrupts the activation capacity of BRCA2. These results suggest that BRCA2 may function as a transcription factor and that elimination of this function may lead to cancer.

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RON LASKEY



KATE BIRD

TORSTEN KRUDE

YUMIKO KUBOTA

CLARE McDONAGH

KATHRIN MARHEINEKE

JACKIE MARR

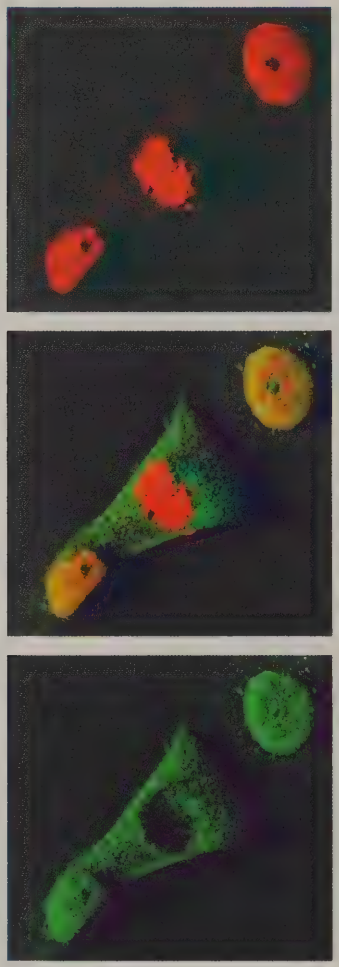
TONY MILLS

CRISTINA PELIZON

PIOTR ROMANOWSKI

KAI STOEBER

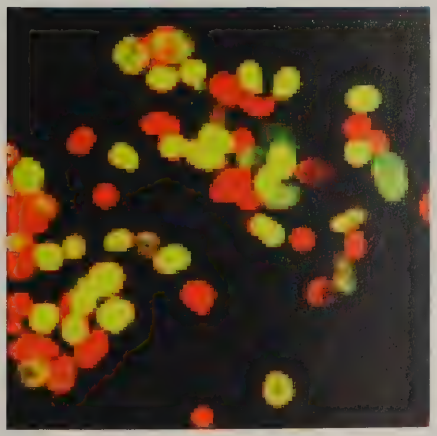
GARETH WILLIAMS



Redistribution of ORC (green) relative to DNA (red) during division of Xenopus cells (Romanowski et al., Ref below page opposite)



Assembly of a "replication licence" from ORC, Cdc6 and MCM proteins



Initiation of DNA replication in a human cell-free system DNA is red, replication is green (red + green = yellow,

We are analysing the control of eukaryotic chromosome replication and the control of nuclear protein import using cell-free systems derived from eggs of Xenopus laevis and, more recently, human cells.

Replication is coupled to the cell cycle so that DNA replicates only once between consecutive divisions. This can be explained by a licensing factor model. We have shown that a family of known proteins, the MCM3 family, are components of the licensing system, and that their binding to chromatin depends on the origin recognition complex ORC and Cdc6.

We have raised antibodies against human and Xenopus Orc2 and Cdc6 as well as to MCM proteins. We are using them to elucidate the roles of these proteins in initiating DNA replication and to assess their value as diagnostic reagents for various forms of cancer.

We have developed novel cell-free systems that initiate DNA replication in human cell extracts in vitro. G1 HeLa nuclei initiate when incubated in S-phase HeLa cytosol together with S-phase nuclei or with an S-phase nuclear extract or with the combination of cdk2 cyclin A and cdk2 cyclin E. We have been able to increase reliability and efficiency by preparing G1 nuclei from 3T3 mouse fibroblasts at specific times after release from quiescence, though these no longer need an S-phase nuclear component. Interestingly, nuclei become competent to replicate at a specific time after release from quiescence, but several hours before the start of S-phase.

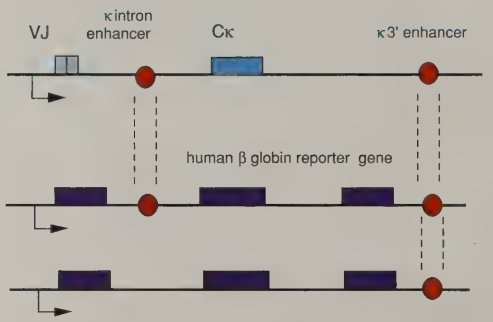
This system should allow similar levels of analysis of control pathways to those achieved previously in Xenopus.

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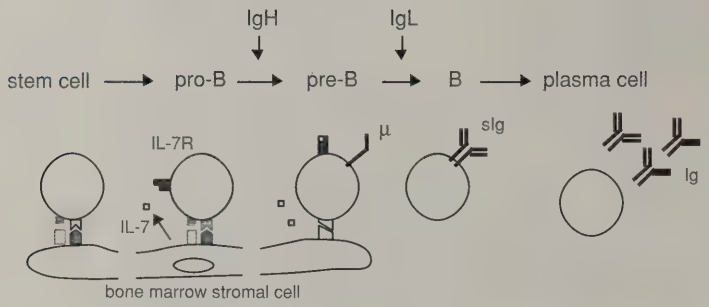
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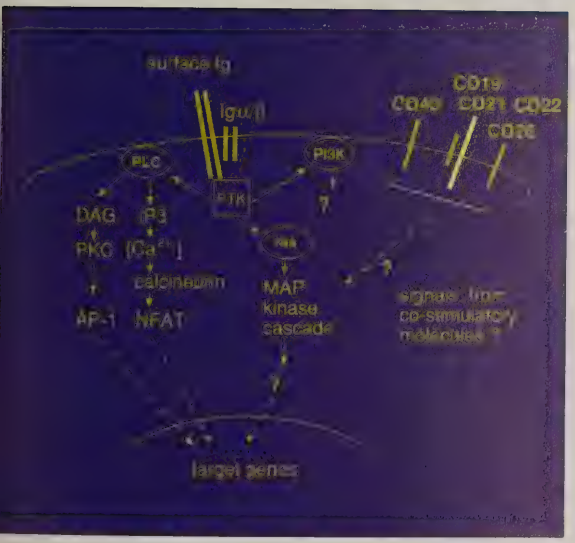
JOHN IRELAND



Structure of constructs introduced into transgenic mice



Schematic representation of B cell development



Crosslinking of surface Ig leads to the activation of NFAT. The role of B cell co-stimulatory signals in this activation cascade is currently being studied

The development of a mature B cell from a haematopoietic stem cell proceeds through a number of distinct stages, defined by the expression of surface markers. Our work has focused on the molecular basis for the tissue-restricted and developmentally controlled expression of some of these surface proteins.

In particular, we have studied the enhancers controlling immunoglobulin (Ig) κ gene expression. The Ig κ3' enhancer plays a role in κ gene rearrangement, expression and somatic hypermutation. We have recently set up a transgenic mouse model to examine the activation of the κ3' enhancer in vivo. These experiments revealed a function of the 3' enhancer early in B cell development and strong inducibility of the 3' enhancer upon activation of a mature B cell. Bacterial lipopolysaccaride which induces rapid B cell proliferation as well as differentiation activates enhancer function, while signals only promoting cellular proliferation, such as crosslinking of the CD40 receptor, had no effect. Enhancer induction could also be brought about by treatment with pharmacological agents such as the calcium ionophore ionomycin and PMA. This induction was found to be mediated by a B-cell-specific NFAT complex containing the NFATc, but not the NFATp isoform, suggesting that this widely expressed transcription factor family has distinct functions in different cell types. Furthermore JunB, JunD, cFos and FosB are part of the complex in B cells. We are currently investigating the physiologic signals, such as crosslinking of cell surface molecules, and the subsequent signalling pathways that play a role in the induction of either the NFAT transcription factor complex or κ3' enhancer function itself.

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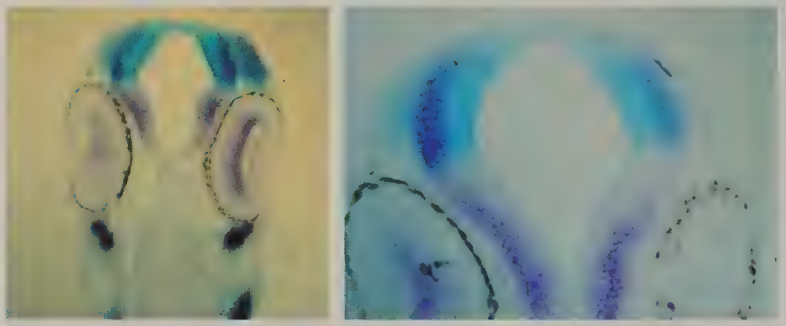


CATHERINE BOURGUIGNON

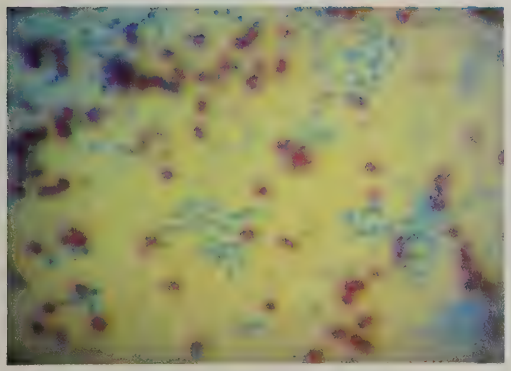
STEVE DAVISON



Double in situ hybridisation showing XBF-1 expression (blue) in the central nervous system of a tadpole in relation to N-tubulin, a neuronal differentiation marker (purple).



Sections through the head of the tadpole shown above. XBF-1 is expressed in undifferentiated progenitors (blue) while N-tubulin is expressed in differentiated neurons (purple).



Misexpressing XBF-1 RNA in the Xenopus embryo induces ectopic neuronal differentiation. Blue staining: XBF-1/lacZ expressing cells, detected by X-gal staining. Purple staining: N-tubulin expressing cells, detected by in situ hybridisation.

Neural induction in Xenopus embryos requires inductive interactions between the ectoderm and a mesodermal region of the embryo, called Spemann's organiser. A process that is closely linked to neural induction is the process of regionalisation or patterning, whereby the neural ectoderm is divided into regions with distinct developmental fates. We have shown that this patterning process controls the position and timing of primary neuron differentiation within the neural plate.We are interested in identifying the molecular nature of the signals that are involved in patterning and neurogenesis and to understand how these two processes are integrated. By expressing a dominant negative form of a retinoic acid receptor in whole Xenopus embryos we have shown that retinoid signalling is necessary in vivo for correct anteroposterior patterning and neuronal differentiation.

We are currently working to identify additional factors and to this end, we have designed functional screens that will specifically identify signals or intracellular determinants that posteriorise and/or induce neuronal differentiation. In addition, we have characterised a number of regionally-restricted transcription factors such as XBF-1, a telencephalon-specific, winged-helix transcription factor and Xbr-1, a novel homeobox gene, and we are currently manipulating the expression of these genes to investigate their role in patterning and neurogenesis.

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JONATHON PINES



PAUL CLUTI

NICOLE DEN ELZEN

NOBUAKI FURUNO

ANJA HAGTING

MARK LACKMAN

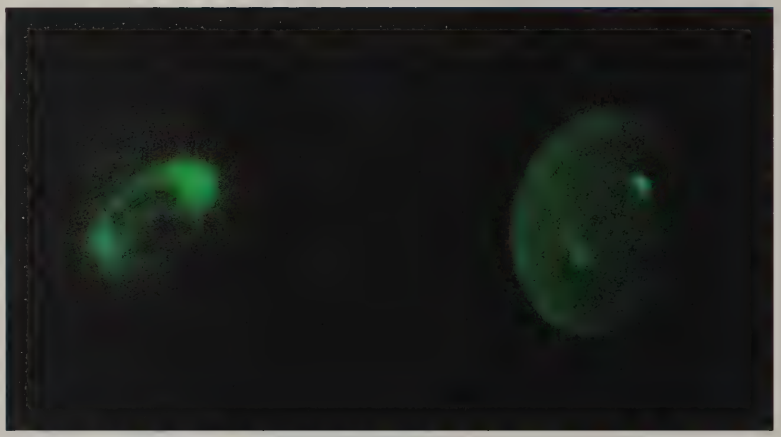
CHRISTINA KARLSSON

TUNKIAT KO

LUCY PERKINS

KAREN SIMPSON

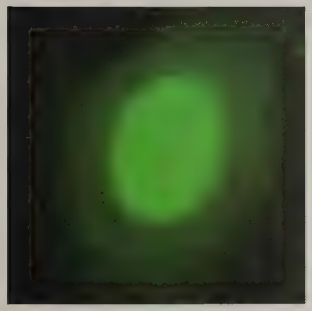
JEAN YVES THURET



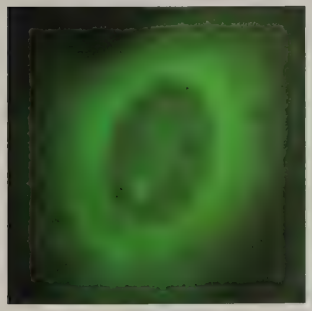
Cyclin B1 and and Cyclin B1-GFP bind to the mitotic spindle.
Left: Endogenous cyclin B1 visualised by immunofluorescence. Right: Cyclin B1-GFP visualised in a living metaphase cell



4 min



6 min



12 min

Cyclin B1-GFP is exported from the nucleus Cyclin B1-GFP purified from baculovirus infected cells was injected into a HeLa cell nucleus and then imaged with a cooled slow scan CCD camera

The dramatic changes in the architecture of the cell as it prepares to divide are orchestrated by the cyclin-dependent kinases (CDKs) and their cyclin partners. Our goal is to determine how cyclin-CDK activities are coordinated in space and time to reorganise the cell at mitosis, and in particular, how cyclins localise their CDKs to specific subcellular structures – including the mitotic spindle and the Golgi apparatus.

We are studying the dynamic behaviour of the mitotic cyclins during cell division in real time, in living cells, using chimaeras between cyclins and GFP. We are visualising these proteins and their effect on cell architecture by time-lapse fluorescence and DIC video microscopy. We are defining the domains of the B-type cyclins that target them to the spindle and the Golgi, and the interactions between the cyclin-CDKs and other components of the cell cycle machinery. We are also using this assay to try to understand the mitotic role of cyclin A.

One of the first events at the start of cell division is the rapid nuclear entry of cyclin B1-cdc2. This translocation is conserved in animal cells and may be part of the regulation of mitosis. We have found that the cyclin B1-cdc2 complex is kept out of the nucleus until prophase by a nuclear export sequence. We also have evidence that phosphorylation overcomes this to cause cyclin B1-cdc2 to move into the nucleus at mitosis. Moreover, in collaboration with Ron Laskey's group, we have found that cyclin-CDK complexes form a novel nuclear targeting signal that is recognised and transported into the nucleus by the importin β family, independent of importin α. We now wish to identify which member of the importin β family acts as the receptor, and which domains of the cyclin-CDK complex target it to the nucleus.

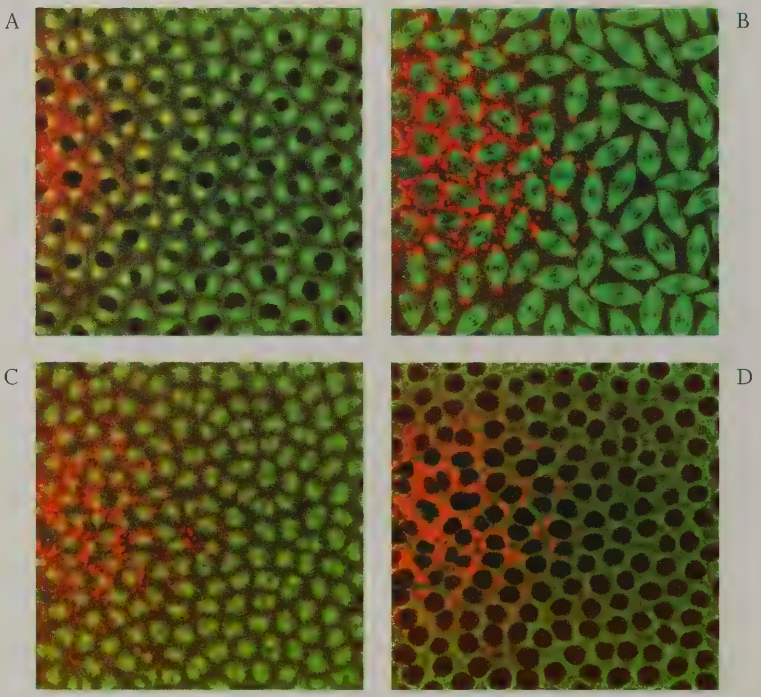
Pines, J. and Hunter, T. (1994). 'The differential localisation of human cyclins A and B1 is due to a cytoplasmic retention region in cyclin B1'. **EMBO J. 13, 3772-3781**.

Jackman, M., Firth, M., and Pines, J. (1995). 'Human cyclins B1 and B2 are localised to strikingly different structures: B1 to microtubules, B2 primarily to the Golgi apparatus'. **EMBO J. 14, 1646-1654**.

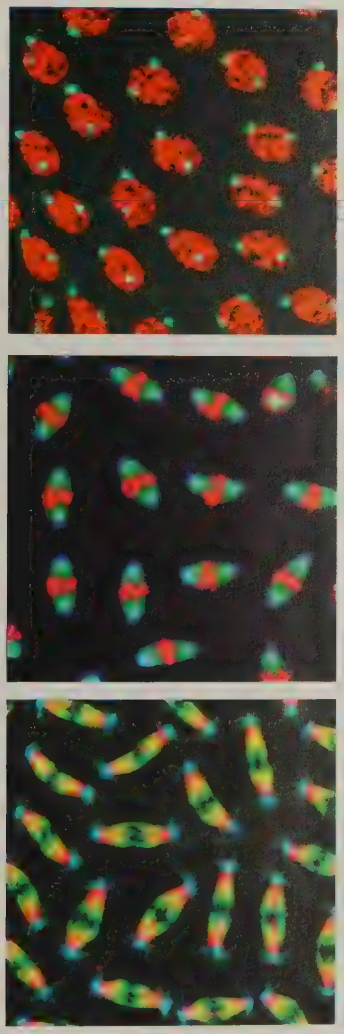
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CENTROSOMES
AND CANCER
GIRTON COLLEGE
DEPARTMENT OF
ZOOLOGY



Anti MA8 antibodies were injected into living embryos and the antibodies (red) and microtubules (green) followed in real time. (A) In interphase, antibodies bind to the centrosome but microtubules appear to be unperturbed. (B) In metaphase, the spindle is short and highly abnormal in the regions of high antibody concentration. In (C) and (D) (two different focal planes at the same time point) the embryo has returned to interphase, the microtubules (C) look relatively normal, but the chromosomes have failed to segregate properly in the regions where spindle formation was abnormal.



The distribution of the MA8 protein (Blue), microtubules (Green) and DNA (Red) in early embryos at interphase (A), metaphase (B) and anaphase (C). The MA8 protein is located at the centrosome throughout the cell cycle.

The centrosome is the main microtubule organising centre in animal cells. Despite its central role in organising many cellular events, very little is known about how the centrosome functions. We have taken a reductionist approach to this problem, and have isolated a number of proteins that can bind to microtubules in vitro and are associated with centrosomes in vivo. We hope that by studying these proteins we can gain a better understanding of how the centrosome functions at the molecular level.

One of these proteins is a novel protein kinase called LK6 that is located in the centrosome throughout the cell cycle. This protein is rapidly turned over in the embryo. Flies overexpressing the LK6 kinase are very unhealthy and there are a variety of defects in microtubule organisation in the early embryos of these flies. The mammalian kinases Mnk1 and Mnk2 are highly related to LK6 within the kinase domain. Both of these kinases are directly activated by MAP kinase, and it appears that LK6 is also directly activated by MAP kinase. A second protein, MA8, is localised to the centrosome throughout the cell cycle (see figure). Injection of anti-MA8 antibodies into early embryos dramatically inhibits mitotic spindle formation, and our current hypothesis is that MA8 is required to stabilise the microtubules in the spindle (see figure). A third protein, CP60, is located mainly in the nucleus in interphase and relocates to the centrosome during mitosis. Phosphorylation by cdc2/cyclin B regulates the ability of this protein to interact with microtubules in vitro, and we have now shown that these putative cdc2 phosphorylation sites are important in regulating the microtubule-binding properties of CP60 in vivo.

We are particularly interested in how centrosome and microtubule behaviour are regulated during the cell cycle, and we have recently developed a novel genetic screen to look for mutations that effect microtubule stability. We hope that a combination of these biochemical and genetic approaches will allow us to identify many of the proteins involved in centrosome function.

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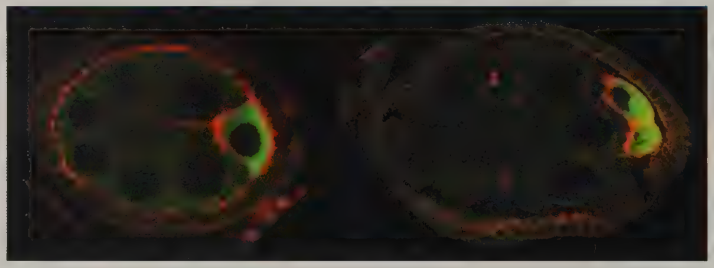
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RACHEL SMITH

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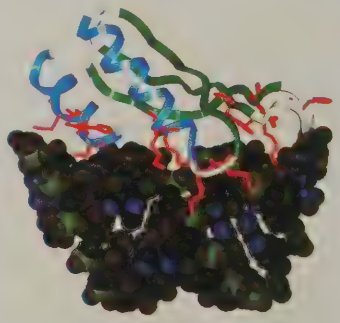
LUCIE WHITEHEAD

A



B

A) Wildtype egg chamber showing the accumulation of BicD protein (green) in a single germline cell, the oocyte.
B) spn-D spn-A double mutant egg chamber in which two cells accumulate BicD protein and develop as oocytes. This phenotype shows that the spn genes are required for the first symmetry-breaking step in oogenesis, the selection of one of the two pro-oocytes to become the oocyte



A model for how a single double-stranded RNA binding domain from Staufen protein contacts dsRNA. The backbone of the domain is shown as a ribbon with the α helices in blue, β sheets in green, and loops in white. The side chains of the amino acids that are required for RNA-binding are shown in red and project from one side of the domain. The model shows how these side chains might contact a 12 base pair region of dsRNA (bottom)



The accumulation of gurken mRNA in the dorsal/anterior corner of the oocyte establishes dorsal-ventral polarity, while the localisation of bicoid and oskar mRNAs to opposite poles determines the anterior-posterior axis.

The intracellular localisation of mRNAs is a general mechanism to target proteins to the regions of a cell where they are required, and plays an important role in the polarisation of many cell types. A striking example of this phenomenon is provided by the *Drosophila* oocyte, where the localisation of *bicoid*, *oskar*, and *gurken* mRNAs to three distinct positions within the cell determines the polarity of the anterior-posterior and dorsal-ventral axes of the embryo. We are using a combination of molecular, cell-biological and genetic techniques to investigate the mechanism of mRNA localisation. In addition, we are studying how the two axes of the oocyte become polarised to define the destination of these transcripts, in order to understand the origin of polarity in *Drosophila* development.

1) We have shown that the dsRNA-binding protein Staufen is required for the localisation and translational control of both *bicoid* and *oskar* mRNAs, and co-localises with each transcript. Our aim is to identify how Staufen interacts with two different mRNAs, and to understand what role this protein plays in mRNA transport.

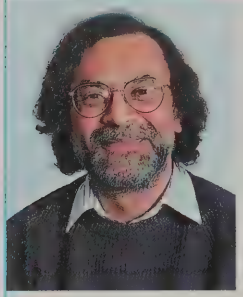
2) Since we have so far identified only a few of the factors that are involved in mRNA localisation, we are using both biochemical and genetic approaches to find the missing genes in this pathway.

3) We have recently shown that there are three symmetry-breaking steps that lead to the polarisation of the oocyte, and have identified a group of genes that are involved in each of these events. We are now cloning two of these genes to determine the molecular link between these steps, and are analysing in detail how the oocyte reaches the posterior of the egg chamber, as this generates the first anterior-posterior polarity during oogenesis.

González-Reyes, A., Elliott, H. and St Johnston, D. (1997). Oocyte determination and the origin of polarity in *Drosophila*: the role of the *spindle* genes. **Development 124: 4927–4937.**

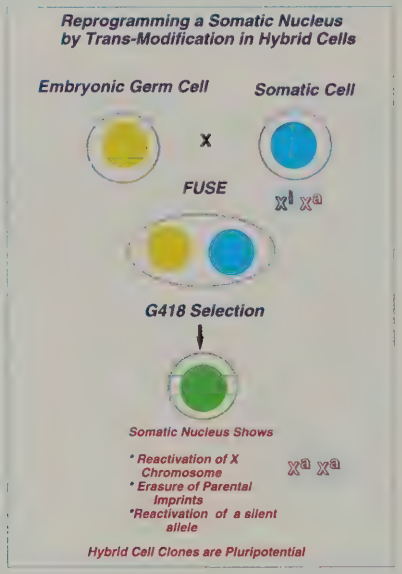
Micklem, D. R., Dasgupta, R., Elliott, H., Gergely, F., Davidson, C., Brand, A., González-Reyes, A., and St Johnston, D. (1997). The mago nashi gene is required for the polarisation of the oocyte and the formation of perpendicular axes in Drosophila. **Current Biology 7, 468–478.**

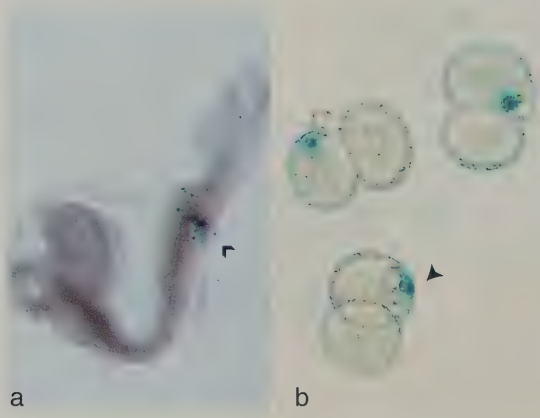
González-Reyes, A., Elliot, H. and St Johnston, D. (1995). Polarisation of both major body axes in *Drosophila* by *gurken-torpedo* signalling. **Nature, 375: 654–658.**



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In the embryonic germ cell-somatic cell hybrids, the somatic cell is fully reprogrammed by erasure of parental imprints. The hybrid cells are pluripotential as they differentiate into many different cell types after introduction into a normal host blastocyst.





a) Primordial germ cells detected at the base of the allantois and hindgut pocket in head fold stage in the Oct4-LacZ transgenic mouse embryo. Both a maternal and a paternal genome are apparently sufficient individually for the development of the germ line. b) An asymmetrically localised lacz+ve structure was detected in early primordial germ cells of ROSA 26 transgenic mice. This structure persists in a single blastomere throughout preimplantation development to the blastocyst stage.

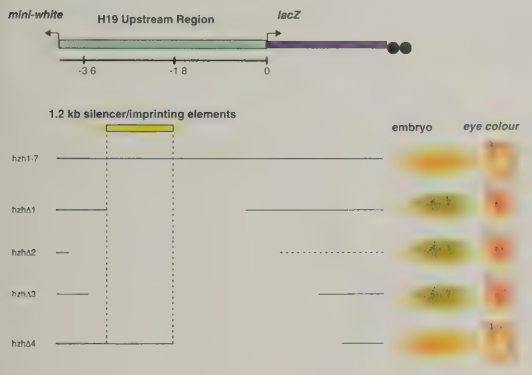
Mammalian development is uniquely governed by the complementary functions of parental genomes because these inherit specific epigenotypes from the maternal and paternal germ line. The germ line-specific epigenetic modifications confer appropriate preferential expression on one parental allele of certain genes, called the imprinted genes.

Development of primordial germ cells (PGC) is accompanied first with the erasure of previous epigenetic modifications. This was deduced from transplantation of a PGC nucleus into an enucleated oocytes that resulted in a conceptus with an unusual phenotype, consistent with the absence of parental imprints. Secondly, a striking trans-modification activity was detected in the pluripotent germ cell-somatic cell hybrids resulting in a complete reprogramming and loss of parental imprints from the somatic nucleus.

Specific *cis* elements are associated with imprinted genes and are required for the initiation of heritable epigenetic modifications in the germ line. One such *cis* regulatory element was shown to cause imprinting of an H19 reporter transgene. This *cis* element also acts as a gene silencer in *Drosophila*, suggesting conservation of certain epigenetic mechanisms. Conditional deletion of this *cis* element, together with genes encoding *trans*-acting factors in germ cells, gametes and embryos, will establish its precise function during the imprinting cycle.

Investigations on the developmental roles of novel imprinted genes Nnat, Peg3, Peg1 and p57kip2, continue and demonstrate that some of these genes also govern adult behaviour.

H19 imprinting cis element functions as a gene silencer in Drosophila.



The H19 imprinted gene shows preferential expression of the maternal allele. An imprinting cis element has been detected in the upstream region between -2 and -4kb. The transgene when introduced into Drosophila led to the identification of a 1.2kb cis element which acts as a bidirectional gene silencer. The overlap between the imprinting/silencer element suggests conservation of certain epigenetic mechanisms in these organisms.

Ainscough J F-X, Koide T, Tada M, Barton S C, Surani M A (1997) Imprinting of Igf2 and H19 from a 130kb YAC transgene. **Development 124, 3621-3632.**

Narasimha, M., Barton, S. C., Surani, M. A. (1997) The role of the paternal genome in the development of the mouse germ line. **Current Biology. 7, 881-884.**

Tada M., Tada T, Lefebvre L, Barton S C, Surani M. A. (1997) Embryonic germ cells induce epigenetic reprogramming of somatic nucleus in hybrid cells. **EMBO J 16, 6510-6520.**



CAROLINE WATERS

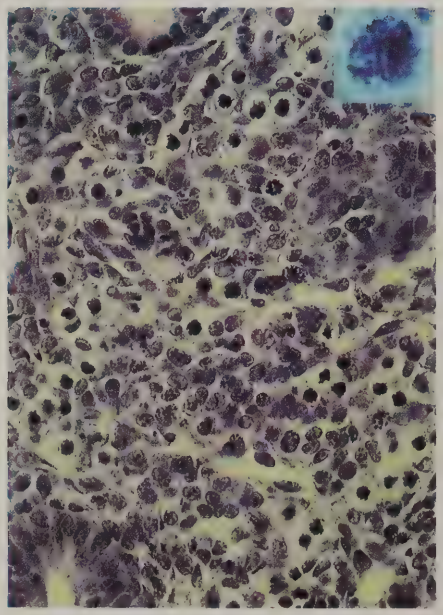
Sexual differentiation in primordial germ cells is initiated only after the germ cells have colonised the embryonic gonads. In female embryos the germ cells then enter meiotic prophase and develop as oocytes. At the same time the germ cells in male embryos enter mitotic arrest. They do not start dividing again until after birth, and the first spermatogenic cells do not enter meiosis until a week later.

If however the male gonad is disaggregated and reaggregated at a stage prior to the time when the germ cells would enter mitotic arrest, they instead enter meiosis and develop as oocytes. We are examining gene expression with and without the disaggregation/reaggregation step, in an attempt to identify the gene or genes responsible for either activating the spermatogenic pathway or inhibiting entry into meiosis.

We are also studying the differences between primordial germ cells and the stem cell (EG cell) lines that germ cells can give rise to in culture, as well as embryonic stem cells (ES cell lines).

McLaren, A. (1997). A note on "totipotency". **Biomedical Ethics, 2, 1**.

McLaren, A., and Southee, D. (1997). Entry of mouse embryonic germ cells into meiosis. **Dev. Biol. 187, 107-113**.



The 11.5 dpc genital ridge from male embryo reaggregated and cultured for 5 days (x450) Note numerous germ cells in meiotic prophase. Inset: high power view of meiotic germ cell (x1500).

CATEGORIES OF APPOINTMENT

Principal Group Leader	Professor / Reader / Lecturer Level
Younger Group Leader	5 year grant-funded appointment (maximum 10 years)
Career Development Fellow	4 year grant-funded appointment
Independent Senior Research Associate	3 year grant-funded appointment
Research Associate / Fellow	Postdoctoral, within individual groups, appointed by the group leader
Graduate Student	3 year studentship within individual groups, mainly grant-funded
Research Assistant	Post-graduate, within individual groups, mainly grant-funded
Research Technician	Within individual groups, mainly grant-funded
Laboratory Assistant	Within individual groups or part of Core support; grant-funded

POSTGRADUATE OPPORTUNITIES

As part of the University of Cambridge, the Institute welcomes enquiries from prospective graduate students. we have a thriving population of graduates who contribute greatly,. not only to the stimulating research environment, but also to the life of the Institute as a whole. Additionally, graduates become members of a Biological or Medical Sciences Department with which their group is affiliated.

Graduate studentships are supposed mainly by the Wellcome Trust or the Cancer Research Campaign but additional sponsorship may be applied for from a variety od sources, including the Government Research Councils.

Applicants should write, in the first instance, to the leader of the group whose work interests them.

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To be appointed
Media Technician

KENNETH WILLIAMS
Media Technician

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MARGARET THODAY
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JANIS ABBOTT

INSTITUTE PUBLICATIONS

AMAYA GROUP

BRANNON, M., GOMPERTS, M., SUMOY, L., MOON, R.T., AND KIMELMAN, D. (1997). A b-catenin/Xtcf-3 complex binds to the siamois promoter to regulate dorsal axis specification in Xenopus. **Genes Dev. 11,** 2359-2370.

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ABOUHEIF, E., AKAM, M., DICKINSON, W.J., HOLLAND, P.W.H., MEYER, A., PATEL, N.H., RAFF, R.A., ROTH, V.L. AND WRAY, G.A. (1997). Homology and developmental genes. **Trends in Genetics 13,** 432-433.

AKAM, M. (1997). Hox genes, homeosis and the evolution of segment identity: no need for hopeless monsters. **Int. J. Dev. Biol.** (in press).

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HO, K., DUNIN-BORKOWSKI, O.M., AND AKAM, M. (1997). Cellularization in locust embryos occurs before blastoderm formation. **Development 124,** 2761-2768.

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HIDALGO, A. AND BRAND, A.H. (1997). Targeted neuronal ablation: the role of pioneer neurons in guidance and fasciculation in the CNS of Drosophila. **Development 124,** 3253-3262.

MICKLEM, D.R., DASGUPTA, R., ELLIOTT, H., GERGELY, F., DAVIDSON, C., BRAND, A., GONZALEZ-REYES, A. AND ST. JOHNSTON, D. (1997). The mago nashi gene is required for the polarisation of the oocyte and the formation of perpendicular axes in Drosophila. **Current Biology 7,** 468-478.

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MARTIN-BERMUDO, M.D. AND BROWN, N.H. (1996). Intracellular signals direct integrin localization to sites of function in embryonic muscles. **J. Cell Biol. 134,** 217-226.

MARTIN-BERMUDO, M.D., DUNIN-BORKOWSKI, O.M. AND BROWN, N.H. (1997). Specificity of PS integrin function during embryogenesis resides in the a subunit extracellular domain. **EMBO J. 16,** 4184-4193.

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OTHER ACTIVITIES

CHARLES FFRENCH-CONSTANT is a Consultant in Medical Genetics at Addenbrooke's Hospital, Cambridge.

JOHN GURDON is currently Vice-Councillor of the Council of the Cancer Research Campaign, and is a Governor of the Wellcome Trust.

STEVE JACKSON is a member of the Biochemical Society Nucleic Acids and Molecular Biology Group Committee, the Biochemical Society Council, and the European Molecular Biology Organization.

RON LASKEY is President of the British Society of Cell Biology, a member of the Cancer Research Campaign Scientific Committee, and a Trustee of Strangeways Research Laboratories.

ANNE McCLAREN is a member of the Advisory Boards of the Human Fertilization and Embryology Authority, the Nuffield Bioethics Council, and Ethical Implications of Biotechnology – advisory group to the European Commission.

DANIEL ST JOHNSTON is a Board Member of the British Society of Developmental Biology, and the Company of Biologists.

HONOURS AND AWARDS

JOHN GURDON special lectures: the Reginald G Harris Memorial Lecture, Cold Spring Harbor, USA; the Royal Society of Ophthalmologists' Edridge Green Medal Lecture, Birmingham, England; the Linacre Lecture, St John's College, Cambridge, England; and the Ida Beam Distinguished Lecture Series, the University of Iowa, USA.

RON LASKEY received the CIBA medal of the Biochemical Society and was awarded the Feldberg Prize and the 1998 Louis-Jeantet Prize for Medicine (Switzerland).

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